Genetic Determinants of Unruptured Intracranial Aneurysms in the General Population

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***Background and Purpose*—**Genome-wide association studies have identified single-nucleotide polymorphisms (SNPs) for intracranial aneurysms in clinical samples. In addition, SNPs have been discovered for blood pressure, one of the strongest risk factors for intracranial aneurysms. We studied the role of these genetic variants on occurrence and size of unruptured intracranial aneurysms, discovered incidentally in a general community-dwelling population.

***Methods*—**In 4890 asymptomatic participants from the Rotterdam Study, 120 intracranial aneurysms were identified on brain imaging and segmented for maximum diameter and volume. Genetic risk scores (GRS) were calculated for intracranial aneurysms (10 SNPs), systolic blood pressure (33 SNPs), and diastolic blood pressure (41 SNPs).

***Results*—**The GRS for intracranial aneurysms was not statistically significantly associated with presence of aneurysms in this population (OR, 1.16; 95% CI, 0.96–1.40; *P*=0.119), but showed a significant association with both maximum diameter (difference in log-transformed mm per SD increase of GRS, 0.10; 95% CI, 0.02–0.19; *P*=0.018) and volume (difference in log-transformed µL per SD increase of GRS, 0.21; 95% CI, 0.01–0.41; *P*=0.040) of aneurysms. GRSs for blood pressures were associated with neither presence nor size of aneurysms.

***Conclusions*—**Genetic variants previously identified for intracranial aneurysms in clinical studies relate to the size rather than the presence of incidentally discovered, unruptured intracranial aneurysms in the general population. **(*Stroke*. 2015;46:2961-2964. DOI:10.1161/STROKEAHA.115.010414.)**

Key Words: aneurysm ■ epidemiology ■ genetics ■ magnetic resonance imaging ■ stroke

Unruptured intracranial aneurysms are incidentally discovered in imaging studies in ≈2% of the general population.[1] Rupture of an intracranial aneurysm can result in a nontraumatic subarachnoid hemorrhage (SAH), an acute condition with high morbidity and mortality rates. For early risk stratification and potential treatment, it is, therefore, important to better understand the pathophysiology of aneurysm development.

Several risk factors for ruptured intracranial aneurysms have been identified, including age, sex, smoking, aneurysm size, and location.[2–4] In addition, an important modifiable risk factor for ruptured intracranial aneurysms is hypertension.[5] Less is known about risk factors for development of intracranial aneurysms, although there is some overlap with risk factors for rupture, including sex, smoking, and hypertension.[6,7] Genetic factors also play an important role in intracranial aneurysms, which is evidenced by the fact that persons with a positive family history have a higher risk of developing intracranial aneurysms compared with the general population.[8] More recently, genome-wide association studies have identified multiple single-nucleotide polymorphisms (SNPs) associated with intracranial aneurysms.[9] Importantly, most studies investigating genetics of intracranial aneurysms have done so in a clinical setting, thereby typically including patients presenting with ruptured aneurysms or persons screened for high familial risk. In such settings, it cannot be discerned whether these SNPs affect the development of intracranial aneurysms or lead to growth and rupture of already present aneurysms. A population-based setting provides a unique opportunity to study the effect of these SNPs on unselected unruptured aneurysms.

We investigated in a community-dwelling population the association of SNPs for intracranial aneurysms with the occurrence and size of unruptured aneurysms, incidentally detected on research imaging. Furthermore, we also studied SNPs for high blood pressure and their association with presence and size of unruptured intracranial aneurysms.

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